C T F A

THE COSMETIC, TOILETRY, AND FRAGRANCE ASSOCIATION

August 12, 2002

E. EDWARD KAVANAUGH
PRESIDENT

Dr. Scott Masten
Office of Chemical Nomination and Selection
NIEHS/NTP
P.O. Box 12233
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Research Triangle Park, North Carolina 27709

Re: Request for Public Comments on Substances Nominated to the National Toxicology Program (NTP) for Toxicological Studies and on Study Recommendations Made by the NTP Interagency Committee for Chemical Evaluation and Coordination (ICCEC) (67 Federal Register 40329: 5-Amino-o-Cresol)

Dear Dr. Masten:

The Cosmetic, Toiletry, and Fragrance Association[1] appreciates the opportunity to provide comments on the above-referenced topic. 5-Amino-o-Cresol (CAS #2835-95-2) is used within the personal care products industry, and thus, toxicological studies on this material are of significant interest to CTFA members.

We recommend that strong consideration be given to a conventional 2-year carcinogenicity bioassay in both rats and mice, with dermal application as the preferred and most relevant route of administration. Additionally, we advocate that such bioassays be preceded by dermal and oral toxicokinetic/ADME studies. The rationale for these recommendations and relevant supporting information is described below.

Exposure and Route: The document outlining the basis of nomination of 5-amino-*o*-cresol for study indicates that it is broadly used as an ingredient in cosmetic hair dyes. Dermal exposure is the most relevant route for this material for both consumers and hairdressers who apply hair dyes. Dermal exposure includes the scalp and the adjacent neck and forehead areas. Hands are another potential source of exposure. However, protective gloves are often worn by both consumers and hairdressers, particularly when dark shades which have the greatest potential for staining the hands and nails, are used. Other parts of the body may be exposed dermally, at least briefly, to very dilute solutions when the excess hair color is rinsed off at the end of the application period.

[1] CTFA is the U.S. national trade association representing the personal care products industry. CTFA is comprised of over 300 active members that produce the vast majority of the cosmetics distributed in the U.S. and that also produce many over-the-counter drugs designed for dermal application. The association also has over 300 associate members that provide raw ingredients and supplies and services to the industry. Many of CTFA's members are international companies that do business in many foreign countries as well.

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Consumer exposure to hair dye products is, in general, relatively brief (20-40 minutes typical application times) and infrequent with intermittent use, at about 4-6 week intervals. Occupational exposure would occur more frequently but would be minimized by regular use of gloves during product application and rinsing.

Under actual hair dyeing conditions, potential systemic exposure for hair dyes is relatively low. Discreet data obtained in human volunteers coloring their hair with a commercial product containing 0.67% ^{14}C-labeled 5-amino-*o*-cresol gave exposures based on 48 hour urinary recovery of about 13.8 ug/kg per application or about 1.38 ug/cm^2 scalp (based on 60 kg body weight and 600 cm^2 scalp area). This was equivalent to about 0.2% of the dose applied to the hair and scalp (Maibach and Wolfram, 1981; Wolfram and Maibach, 1985).

Hair dye absorption has been studied extensively in vitro using rat, monkey, pig and human skin and in vivo using rats monkeys and humans (Dressler, 1999; Beck *et al*, 1994; Steiling *et al*, 2001). These studies indicate that rat skin is generally more permeable to hair dyes than pig or human skin. Topical application of 5-amino-*o*-cresol in a formulation containing 1.0% with other dyes before mixing 1:1 with hydrogen peroxide to rats (amount unspecified) for 30 minutes resulted in a skin penetration equivalent to 3.62 ug/cm^2 and 5.64 ug/cm^2 for male and female rats, respectively (Bartnik *et al*, 1991). The same formulation, at a dose equivalent to 2 mg of 5-amino-*o*-cresol applied to 10 cm^2 clipped rat skin, showed no significant accumulation in any organ (Bartnik *et al*, 1991).

Prior NTP studies on a number of oxidative as well as direct hair dyes have all been conducted by the oral route of administration. However, the relevance of this route for such materials was frequently questioned during the Peer Review process (NTP Technical Reports). Thus, CTFA recommends the dermal route of administration for the present study.

CTFA is aware of member companies' unpublished data indicating 5-amino-*o*-cresol has moderate sensitization potential as measured by the murine local lymph node assay utilizing CBA mice. It will be important to consider this in the design of a dermal bioassay. Dermal range-finding studies in the relevant mouse strain would be informative in this regard. Comparative strain data are available indicating that B6C3F1 mice are among the strains showing responsiveness to moderate or strong sensitizers (Woolhiser *et al*, 2000).

It is important to recognize that 5-amino-*o*-cresol is a colorless hair dye precursor (coupler) which combines with a colorless primary intermediate (e.g., *p*-phenylenediamine, *p*-aminophenol) to form a colored, less soluble, higher molecular weight reaction product which becomes entrapped in the hair fiber. Consequently, the driving concentration of oxidative hair dyes decreases over the exposure period as the precursors are consumed by the reaction process.

Further, the larger reaction product would be less permeable through skin. Absorption of the specific reaction product between 5-amino-*o*-cresol and *p*-aminophenol, equivalent to 0.82 ug/cm^2, was substantially less than the value cited above for 5-amino-*o*-cresol (Tsomi and Kalopissis, 1982). Dermal application of individual dyes may therefore result in overestimation of exposure compared with actual use of formulated products.

Model Choice: Regarding the choice of model for addressing the carcinogenicity of 5-amino-*o*-cresol, it is recommended that a standard dermal carcinogenicity study be

conducted as opposed to the Tg.AC transgenic mouse model. Currently, standard skin painting carcinogenicity testing protocols are available that provide an acceptable assessment of carcinogenic potential, whereas the Tg.AC mouse model is still under development and, therefore, is not an appropriate choice at this time. Consistent with this is the conclusion of the Tg.AC Assay Working Group of the International Life Sciences Institute (ILSI) Health and Environmental Safety Institute (HESI) Alternatives to Carcinogenicity Testing (ACT) program that "there is no evidence that the model can be used alone for this purpose." i.e., for carcinogenicity testing (Eastin *et al*, 2001; Cohen *et al*, 2001).

Additional Studies In addition to the formulation studies cited above, available toxicokinetic/ADME data for 5-amino-*o*-cresol include oral administration of 9.5 mg/kg of the compound to Wistar rats. At 96 hours, 87.5% of the radioactivity was excreted in the urine, 11.1% in feces, with 0.035% remaining in the gastrointestinal tract and 0.267% in the remaining carcass (Gebauer, 1993). Subcutaneous injection at a similar dose (10 mg/kg) resulted in 83% urinary excretion (at 96 hours), with 17.6% in the biliary tract and variable fecal excretion (Gebauer, 1993). Although the quantitative route of excretion appears similar after oral or subcutaneous administration, it is uncertain whether both routes result in similar metabolism.

It can be predicted that 5-amino-*o*-cresol will likely be glucuronidated or sulfated at the phenolic OH group, forming a major metabolite. This is the likely route of urinary elimination following the relatively low systemic exposure that occurs following the topical use of hair dye formulations. In addition, there could be oxidation of the methyl function to the respective alcohol and possibly to the carboxylic acid. It is also possible that the amine function could be conjugated (acetylated) and eliminated. Since there are no data to support these predictions, it is strongly recommended that dermal and, possibly, oral ADME studies be conducted to quantify dermal uptake and distribution of this material and to compare oral and dermal metabolic pathways. The results of such a study would help confirm the suitability of a topical route of administration as the appropriate choice for a carcinogenicity study.

We hope NTP will find these comments useful. CTFA will be most willing to provide further industry input, such as on the selection of vehicle and range-finding dosage levels, during the design phases of the planned studies, as appropriate.

Thank you for your attention to these issues.

Sincerely,

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